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Review

Mechanisms of neuroinflammation and inflammatory mediators involved in brain injury following subarachnoid hemorrhage

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Summary. Subarachnoid hemorrhage (SAH) is a devastating cerebrovascular disorder. Neuroinflammation is a critical cause of brain injury following SAH in both acute and chronic phases. While accumulating evidence has shown that therapies targeting neuroinflammation exerted beneficial effects in experimental SAH, there is little clinical evidence. One of the factors making neuroinflammation complicated is that inflammatory signaling pathways and mediators act as protective or detrimental responses at different phases. In addition, biomarkers to detect neuroinflammation are little known in clinical settings. In this review, first, we discuss how the inflammatory signaling pathways contribute to brain injury and other secondary pathophysiological changes in SAH. Damage-associated molecular patterns arising from mechanical stress, transient global cerebral ischemia, red blood cell breakdown and delayed cerebral ischemia following SAH trigger to activate pattern recognition receptors (PRRs) such as Toll-like receptors, nucleotide-binding oligomerization domain-like receptors, and receptors for advanced glycation end products. Most of PRRs activate common downstream signaling transcriptional factor nuclear factor-κB and mitogen-activated protein kinases, releasing pro-inflammatory mediators and cytokines. Next, we focus on how pro-inflammatory substances play a role during the course of SAH. Finally, we highlight an important inducer of neuroinflammation, matricellular protein (MCP). MCPs are a component of extracellular matrix and exert beneficial and harmful effects through binding to receptors, other matrix proteins, growth factors, and cytokines. Treatment targeting MCPs is being proved efficacious in preclinical models for preventing brain injury including neuroinflammation in SAH. In addition, MCPs may be a candidate of biomarkers predicting brain injury following SAH in clinical settings.

Key words: Neuroinflammation, Early brain injury, Extracellular matrix, Inflammatory mediator, Subarachoid hemorrhage

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Introduction

Aneurysmal subarachnoid hemorrhage (SAH) is one of cerebrovascular diseases with devastating consequences, and triggers a variety of neurovascular events leading to brain injuries in acute and chronic phases (Suarez et al., 2006; van Gijn et al., 2007; Suzuki, 2015). When an intracranial aneurysm ruptures, arterial blood spreads into the subarachnoid space, which leads to rapid elevation of intracranial pressure followed by transient global cerebral ischemia and the primary brain injury. As well as the primary brain injury, mechanical stress arising from arterial bleeding, blood components and their secondary products in the subarachnoid space cause secondary brain injury. Early brain injury (EBI) is the term defined as any kind of

acute secondary pathophysiological events other than iatrogenic ones, which are induced in the brain within the first 72 hours after the onset of SAH (Suzuki, 2015). In clinical settings, at present, few reliable surrogate markers of EBI are available, such as global cerebral edema (Geraghty et al., 2019; Suzuki et al., 2020). From a pathological viewpoint, manifestations of EBI mainly involve neuronal apoptosis and neuroinflammation (Nakano et al., 2019b; Okada et al., 2019a; Sehba et al., 2012). EBI is increasingly recognized to be the primary determinant for poor outcomes, and is also considered to cause delayed cerebral ischemia (DCI) that occurs at days 4 to 14 or later post-SAH (Suzuki et al., 2018). DCI has been shown to occur in 30-40% of patients with SAH (Budohoski et al., 2014). Clinical deterioration caused by DCI is accompanied by focal neurological deficits or a decrease in Glasgow Coma Scale of at least two points for ≥1 h (Geraghty et al., 2019). The pathophysiology of DCI consists of cerebral vasoconstriction and vasospasm-unrelated causes including blood-brain barrier (BBB) disruption, neuronal apoptosis, cortical spreading depolarization, microcirculation disturbance, venous drainage disturbance, and neuroinflammation (Suzuki et al., 2015; Vergouwen et al., 2010).

Treatment for SAH has targeted mainly the prevention of rebleeding of an intracranial aneurysm at an early phase and the prevention or reversal of angiographic vasospasm of the intracranial arteries, which peaks at 5 to 9 days after SAH (Okada and Suzuki 2017; Nakano et al., 2019a, 2020). Early aneurysmal obliteration by clipping or coiling has been established nowadays, but the subsequent anti-vasospastic treatment has been insufficient to achieve better outcomes of patients with SAH (Suzuki 2015). This may be because DCI following EBI and not associated with angiographic vasospasm is an important factor of poor outcomes (Kawakita et al., 2017). Accumulating evidence has shown that neuroinflammation is a pivotal component leading to EBI and DCI following SAH (Provencio and Vora, 2005; Springborg et al., 2007; Makino et al., 2012; Caffes et al., 2015; Suzuki and Kawakita, 2016). Pro-inflammatory mediators and cytokines arising from global cerebral ischemia as well as breakdown products of red blood cells trigger a number of cascades for inflammatory reactions leading to BBB disruption, microvascular disturbance, neuronal apoptosis, and cerebral vasospasm (Suzuki et al., 2015; Lucke-Wold et al., 2016; Okada and Suzuki 2017). BBB disruption allows macrophages and neutrophils to migrate into the brain parenchyma, and resultantly multiple pro-inflammatory substances induced by inflammatory responses are considered to promote further aggravation of neuroinflammation and brain injuries (Lucke-Wold et al., 2016).

Microglia seems to be an essential element to regulate inflammation in the central nervous system (CNS) (Hanafy, 2013; Schallner et al., 2015; Schneider et al., 2015; Wei et al., 2017). Microglia is a resident immune cell in the CNS, serving as an immune responder through altering the morphology and polarization (Aloisi, 2001). Phenotypes of microglia are classified into pro-inflammatory phenotype (M1) and anti-inflammatory phenotype (M2) (Graeber 2010; Murakami et al., 2011; Hu et al., 2012). The M1 phenotype is dominantly polarized in the early phase of SAH and tends to release pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, IL-8, IL-12, and tumor necrosis factor (TNF)-α, and nitric oxide (NO) (Fig. 1), while the M2 phenotype is likely to release anti-inflammatory cytokines and neurotrophic factors such as IL-4, IL-10, IL-13, and transforming growth factor (TGF)-β, promoting inflammatory resolution and tissue repair in the subacute and delayed phases (Graeber, 2010; David and Kroner, 2011; Zheng and Wong, 2017, 2019).

In this review, we focus on inflammatory signaling pathways aggravating brain damage in SAH, and discuss how inflammatory mediators, matricellular proteins (MCPs), contribute to neuroinflammation and subsequent brain injury in acute and chronic phases of SAH.

Possible molecular mechanism of neuroinflammation in an acute phase

Damage-associated molecular patterns (DAMPs) are endogenous molecules released as a result of tissue damage following SAH. DAMPs are localized within a variety of cells or tissues as follows: high-mobility group box 1 proteins (HMGB1s) in nucleus and cytoplasm, S100 proteins in cytoplasm, heat shock proteins (HSPs) in exosomes, adenosine triphosphate (ATP) in mitochondria, MCPs in extracellular matrix, and complements in plasma components (Tang et al., 2013). In addition, bleeding itself and the breakdown and degradation of red blood cells within the subarachnoid space also release DAMPs including hemoglobin, methemoglobin, bilirubin, coagulation factors such as fibrinogen, and more (Geraghty et al., 2019). DAMPs are recognized by a number of pattern recognition receptors, such as Toll-like receptors (TLRs), cytosolic nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) and inflammasome, and receptors for advanced glycation end products (RAGE), and other scavenger receptors, and activate the downstream signaling pathways leading to neuroinflammation in SAH (Fig. 2) (Schaefer, 2014; Chaudhry et al., 2018). Neuroinflammation induces brain tissue injury, and recruits further DAMPs.

TLRs signaling pathway

At present, a total of 11 human and 13 murine TLRs are identified (Buchanan et al., 2010). Of TLRs family members, TLR4 can mediate the strongest inflammatory reaction in SAH (Okada et al., 2019b). A unique feature of TLR4 is to trigger two distinct signaling pathways as

follows: the myeloid differentiation primary response protein 88 (MyD88)-dependent cascades in an acute phase and the Toll receptor-associated activator of interferon (TRIF)-dependent cascades in a late phase (Okada and Suzuki, 2017). In contrast, TLR3 activates downstream signaling solely through the TRIF adaptor (Buchanan et al., 2010). The other TLRs except for TLR3 and TLR4 utilize only the MyD88-dependant cascade (Buchanan et al., 2010). TLR4 is expressed on cell surface in various cells including neurons, astrocytes, microglia, brain capillary endothelial cells, endothelial and smooth muscle cells of cerebral arteries, and peripheral blood cells such as leukocytes, macrophages, and platelets (Buchanan et al., 2010; Okada and Suzuki, 2017). TLR4 is activated by many DAMPs such as extravasated blood components (fibrinogen, and fibrin), red blood cell breakdown products (heme, hemin, and methemoglobin), other intracellular components (HSPs, HMGB1, and S100), and MCPs including tenascin-C (TNC) and galectin-3 (Suzuki 2019). Activation of TLR4 induces pro-inflammatory cytokines and mediators such as TNF-α, ILs (IL-1β, IL-6, IL-8, and IL-12), intercellular adhesion molecule-1, monocyte chemoattractant protein, and matrix metalloproteinase (MMP)-9 via the activation of the adaptor molecule MyD88 and the downstream signaling transcriptional factors nuclear factor (NF)-κB and mitogen-activated protein kinases (MAPKs) (Buchanan et al., 2010; Fang et al., 2013; Kawakita et al., 2017; Okada et al., 2019b). Pro-inflammatory cytokines and mediators upregulate specific cell adhesion molecules on brain capillary endothelial cells and induce neuroinflammation, degradation of brain capillary endothelial basal membrane leading to BBB disruption, and apoptosis of various cells, all of which aggravate EBI after SAH (Kanamaru and Suzuki, 2019; Suzuki et al., 2020). MMP-9 is mainly a proteolytic enzyme, which is involved in inflammatory responses and induced by inflammatory cytokines and reactive oxygen species, and degrades the extracellular matrix of cerebral microvessel basal lamina such as collagen IV, laminin, fibronectin, and inter-endothelial tight junction proteins such as zonula occludens (ZO)-1, causing BBB disruption (Fig. 2) (Guo et al., 2010; Okada et al., 2019b; Peeyush Kumar et al., 2019). Therefore, therapy targeting TLR4 is possibly one of the novel options. Indeed, a recent study demonstrated that a selective TLR4 antagonist attenuated neurobehavioral impairments and prevented BBB disruption via suppression of the expression of MAPK c-Jun N-terminal kinases (JNKs) and MMP-9 in SAH mice (Okada et al., 2019b). On the other hand, the TRIF-dependent pathway may induce interferon regulatory factor-3 as well as NF-κB and MAPKs, releasing interferon-β in a late phase of SAH (Akira and Takeda, 2004; Buchanan et al., 2010). Interferon-β modulates the innate immune responses and exerts both anti-inflammatory and anti-apoptotic effects (Akira and

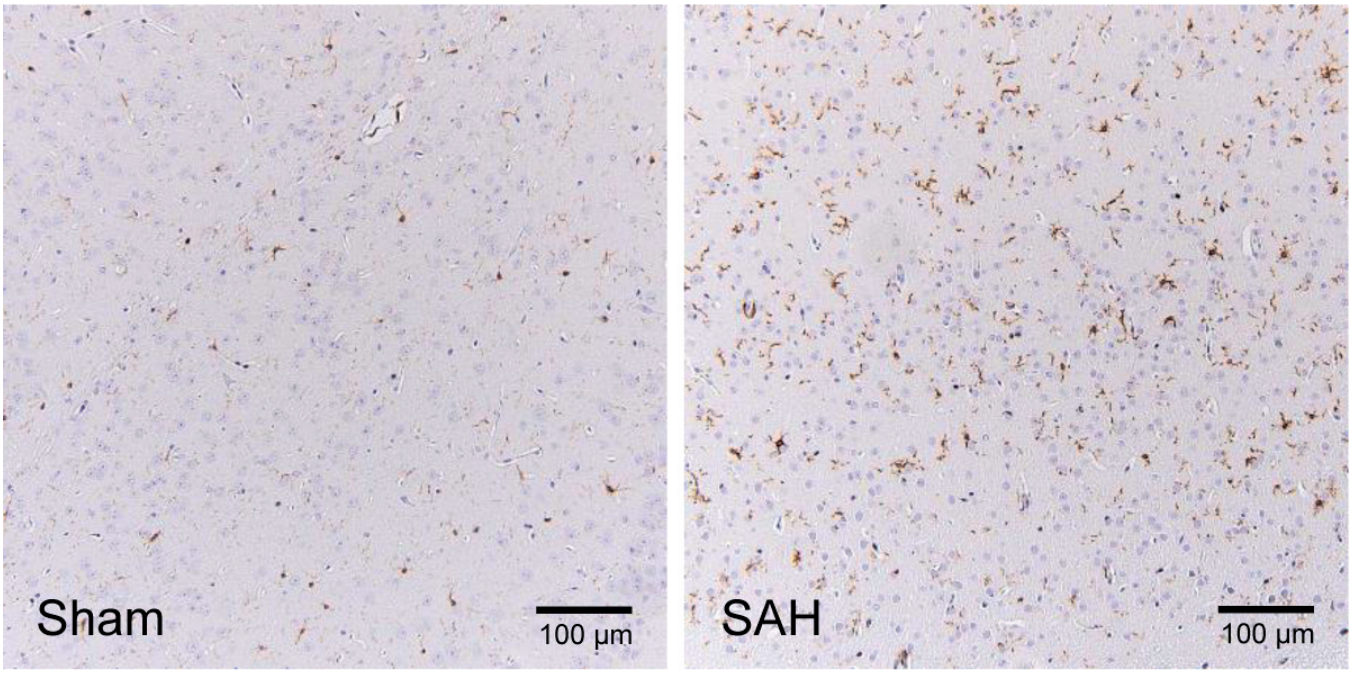

Fig. 1. Immunohistochemical staining for ionized calcium binding adapter molecule 1 (Iba-1) in the left temporal cortex at 1.0 mm posterior to the bregma at 24 h after filament-perforation subarachnoid hemorrhage (SAH) in mice. Compared with sham-operated mice, microglia are increased and activated after SAH.

Takeda, 2004). The ligands of TLR4 interact with the receptor without distinction and induce the same downstream signaling pathways, but the control mechanisms to switch from pro- to anti-inflammatory reactions are poorly understood (Buchanan et al., 2010).

Cytosolic NLRs and inflammasome signaling pathway

Inflammasomes are cytoplasmic multiprotein oligomers and four NLR family members have been described as components of inflammasomes: nucleotide-binding domain and leucine-rich repeat-containing protein (NLRP) 1, NLRP3, NLRP6, and NLR family caspase activation and recruitment domain-containing protein 4 (Schroder and Tschopp, 2010). NLRP3 inflammasome is the best studied one among all kinds of inflammasomes (Abderrazak et al., 2015). Currently, no ligand which directly binds to NLRP3 has been established. However, many molecular mechanisms are associated with NLRP3 activation via cell surface P2X7 receptor (P2X7R), an ATP-gated, non-selective cation channel that belongs to the P2X superfamily (P2X1-7) of purinoreceptors (Abderrazak et al., 2015). P2X7R is abundant in the CNS and widely expressed in neurons and glial cells (Monif et al., 2009; Di Virgilio et al., 2017). The P2X7R is recognized by various non-protein DAMPs including ATP and extracellular matrix hyaluronic acid, and triggers a flux of cations (Na^+, Ca^{2+} and K^+), leading to the activation of caspase-1, which matures IL-1β and IL-18, subsequently contributing to inflammation and neuronal apoptosis (Mariathasan et al., 2006; Lister et al., 2007; Yamasaki et al., 2009; Chen et al., 2013b; Khalafalla et al., 2017; Tang and Illes 2017). Previous studies demonstrated that P2X7R and NLRP3 inflammasome contributed to neuroinflammation after SAH (Chen et al., 2013b; Zhou et al., 2017). Activation of P2X7R can also stimulate another downstream response RhoA, which activates MAPKs signaling pathway including extracellular signal-regulated kinases (ERKs), JNKs, and p38, leading to further aggravation of brain injury including neuroinflammation (Panenka et al., 2001; Papp et al., 2007; Chen et al., 2013a; Feng et al., 2015; Zhao et al., 2016). In parallel, another non-protein DAMP uric acid activates NLRP3 inflammasome (Tang et al., 2013). However, it is currently unclear how uric acid triggers NLRP3 inflammasome activation (Fig. 2) (Tang et al., 2013; Yang et al., 2019b). The findings have suggested that prevention of activation of P2X7R is considered as a potential option for alleviating EBI in SAH. Some inhibitors of P2X7R have been reported to be useful in the prevention of acute neuroinflammation and cell death after SAH (Chen et al., 2013a,b; Feng et al., 2015; Zhao et al., 2016). Chen et al. (2013a,b) demonstrated that a P2X7 antagonist BBG inhibited activation of NLPR3 inflammasome and MAPK p38, and alleviated neurologic deficits, inflammation, and neuronal apoptosis in SAH rats. Zuo et al. (2018) demonstrated that pretreatment with a selective antagonist of P2X7R A438079 reduced inflammation and increased neurogenesis after SAH in mice. Luo et al. (2019) also demonstrated that a specific NLRP3 inhibitor, MCC950, exerted neuroprotective effects via reduction of the infiltration of inflammatory cells in the brain tissues and suppression of the release of pro-inflammatory cytokines such as TNF-α, IL-1ß, and IL-6, and MMP-9 in SAH rats.

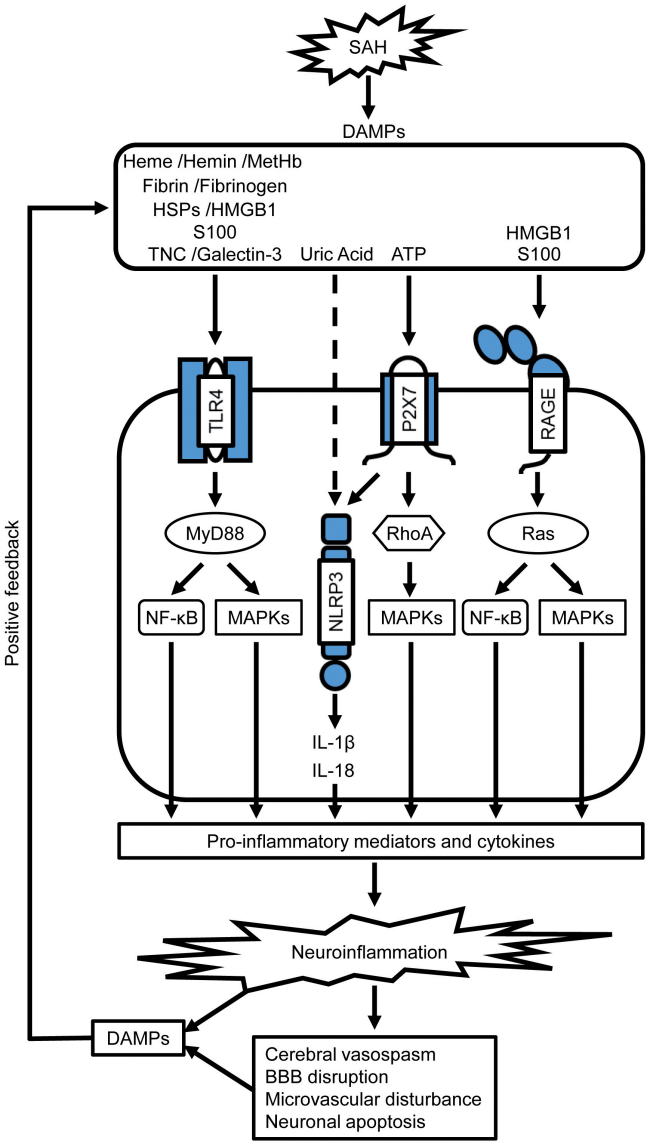

Fig. 2. Possible signaling pathways causing neuroinflammation triggered by pattern recognition receptors in subarachnoid hemorrhage (SAH). ATP, adenosine triphosphate; BBB, blood-brain barrier; DAMPs, damage-associated molecular pattern molecules; Hb, hemoglobin; HMGB1, high mobility group box 1; HSP, heat shock protein; IL, interleukin; MAPK, mitogen-activated protein kinase; MyD88, myeloid differentiation primary-response protein 88; NF-κB, nuclear factor-κB; NLRP3, nucleotide-binding domain and leucine-rich repeat-containing protein 3; P2X7, P2X7 receptor; RAGE, receptor for advanced glycation end products; TNC, tenascin-C ; TLR4, Toll-like receptor 4.

RAGE signaling pathway

RAGE is a transmembrane receptor and contains three parts: an extracellular region that is responsible for ligand interaction through its V domain, a transmembrane domain to anchor the protein to the cell surface, and a cytoplasmic domain that is responsible for downstream signaling (Lee and Park, 2013). RAGE exists in truncated forms following alternative splicing or protease processing (Schaefer, 2014). RAGE expression peaked at 24 h after SAH induction in rats, and increased in neurons, glia, and microglia in the human hippocampus and cortex (Choi et al., 2014; Zheng and Wong, 2017). In addition, the expression of RAGE is upregulated by its ligands such as HMGB1 and S100 family of proteins (Bianchi et al., 2011; Kim et al., 2011). RAGE signaling pathway is possibly responsible for neuroinflammation after SAH (Sparvero et al., 2009; Wang et al., 2017). Its binding to the ligands activates Ras and the downstream signaling NF-κB and MAPKs including p38 and ERK1/2 (Fig. 2) (Rovere-Querini et al., 2004; Sparvero et al., 2009; Bianchi et al., 2011; Kim et al., 2011; Lee and Park 2013; Rani et al., 2014). In contrast, the soluble form of RAGE (sRAGE) corresponds to the extracellular domain of RAGE lacking cytosolic and transmembrane domains, and is able to antagonize full-length RAGE and other receptors by binding to DAMPs and other ligands, inhibiting leukocyte recruitment in a variety of acute and chronic inflammatory conditions (Wang et al., 2017). Administration of recombinant sRAGE reduced neuronal cell death via suppression of inflammation in SAH rats (Wang et al., 2017). In clinical settings, sRAGE levels in the cerebrospinal fluid (CSF) tended to increase in patients with poor outcome between 0 and 3 days after SAH (Sokół et al., 2017). The findings suggest that ligands of RAGE induced by SAH may bind to not only full-length RAGE, but also sRAGE. Further investigations are expected to elucidate the relationships between RAGE and post-SAH brain injury, and the mechanisms.

Possible molecular mechanisms of neuroinflammation in subacute and late phases

Inflammation plays important roles in mediating DCI caused by cerebrovascular spasm, BBB disruption, thrombosis, and recurrent waves of spreading depolarization in the subacute and late stages (Vergouwen et al., 2010). Both cellular and molecular components take part in the inflammatory modulation in the phase after SAH (Zheng and Wong, 2017). Peripheral immune cells such as macrophages and neutrophils are trapped in the subarachnoid perivascular space owing to stagnation of CSF flow, and release MMPs such as MMP-9 (Mehta et al., 2013), which destroy the BBB and allow the immune cells in the perivascular space to migrate into the brain parenchyma, causing more releases of MMP-9 and further disruption of the BBB (Guo et al., 2010; Peeyush Kumar et al., 2019). Macrophages and neutrophils migrating in the brain parenchyma due to BBB disruption also undergo degranulation (Guo et al., 2010; Peeyush Kumar et al., 2019), resulting in releases of various inflammatory factors including endothelins (ETs) and reactive oxygen species (Zheng and Wong, 2017). These factors can cause inflammation-induced vasoconstriction, meningitis, and vasogenic brain edema (Li et al., 2014). In addition, microglia is highly polarized longer than 3 days after SAH in both animals and humans (Zheng and Wong, 2019). M1 phenotype-associated markers CD68 and CD86 remained highly expressed at least until 72 h in post-SAH rats (Li et al., 2018). In post-mortem analyses of tissues, the expression of activated microglial marker CD68 increased between 5 and 15 days after clinical SAH (Schneider et al., 2015), and both pro-inflammatory and anti-inflammatory mediators were detected in the CSF of SAH patients at 7 days post-SAH (Greenhalgh et al., 2012). The pro-inflammatory mediators and cytokines induce brain injury consisting of neuronal apoptosis, microthrombosis and cerebral vasoconstriction, and further activate peripheral immune cells via upregulation of cellular adhesion molecules (Geraghty et al., 2019). C-reactive protein (CRP), a sensitive and unspecific systemic inflammatory marker, is increased after 3 days of onset in both serum and CSF in patients with aneurysmal SAH (Kacira et al., 2007). CRP is stimulated to express by pro-inflammatory cytokine IL-6, and its serum and CSF levels correlated with the development of cerebral vasospasm and poor outcome after SAH (Fountas et al., 2009). In contrast, TLR4 may regulate inflammation via TRIF-dependent signaling pathways in the late phase of SAH, although the exact functions of TLR4 in the late phase are unclear (Okada and Suzuki, 2017).

Inflammatory mediators and cytokines

Pro-inflammatory cytokines including IL-1β, IL-6, IL-8, TNF-α, and monocyte chemoattractant protein-1 are reported to be elevated in serum and CSF in experimental models and patients with vasospasm, though the evidence is conflicting and inconsistent (Hopkins et al., 2012; Miller et al., 2014). IL-1β and IL-6 levels were elevated in CSF within the first 72 h of SAH in a clinical setting (Hendryk et al., 2003). Following stimulation with IL-1β, IL-1 receptor recruits the adaptor molecule MyD88, and the receptor-adaptor complex induces NF-κB signaling pathway (Sobowale et al., 2016). In parallel, the complex also activates MAPKs signaling pathway including JNK and p38 (Sobowale et al., 2016). In addition, IL-1 upregulates the expression of IL-6, which binds to IL-6 receptor and activates a signal transducer and activator of transcription (STAT) 3, followed by inflammatory responses and the development of vasospasm in the CNS (Sobowale et al., 2016). In experimental settings, a study demonstrated that neutralizing antibody for IL-6 exerted

inhibitory effects against cerebral vasospasm in rats (Bowman et al., 2004). Simultaneously with increases in pro-inflammatory cytokines, elevation of endogenous IL-1 receptor antagonist (IL-1Ra) has been verified in CSF of SAH patients with poor clinical conditions on admission, and higher IL-1Ra levels in CSF resulted in poor outcomes (Zheng and Wong, 2017). Previous studies suggested that IL-1Ra exerted neuroprotective effects and that the treatment with exogenous IL-1Ra is a therapeutic candidate against neuroinflammation that is induced by SAH (Greenhalgh et al., 2012; Singh et al., 2014; Galea et al., 2018). Subcutaneous administration of IL-1Ra reduced neuroinflammation and BBB disruption in SAH rats (Greenhalgh et al., 2012). In clinical settings, Singh et al. (2014) demonstrated that intravenous IL-1Ra tended to reduce the concentration of IL-6 in CSF and plasma of SAH patients, although the study was insufficient to achieve statistical significance owing to low enrollment. However, subcutaneous administration of IL-1Ra in patients with SAH reduced plasma concentrations of IL-6, fibrinogen, and CRP between 3 and 8 days post-onset in randomized controlled trials (Galea et al., 2018). On the other hand, TNF-α levels were correlated with the severity of vasospasm among patients with severe SAH, and higher serum monocyte chemoattractant protein-1 levels were associated with poor outcome but not the severity of vasospasm (Miller et al., 2014). A couple of experimental studies demonstrated the beneficial effects of TNF-α inhibitors in SAH (Vecchione et al., 2009; Ma et al., 2018). Vecchione et al. (2009) showed that a TNF-α inhibitor infliximab attenuated vasospasm and brain injury in SAH mice. Ma et al. (2018) showed that anti-TNF-α antibody attenuated neuronal apoptosis by inhibiting MAPK ERK1/2 in SAH rats.

As acute mediators of inflammation and cellular adhesion molecules, the selectin family is also involved in neuroinflammation after SAH (Yang et al., 2019a). The selectin family consists of three members: leukocyte- (L-) selectin, endothelial- (E-) selectin, and platelet- (P-) selectin (Miller et al., 2014). The selectin family induces binding and migration of leukocytes to vascular endothelium through injured tissues (Yang et al., 2019a). L-selectin and E-selectin are constitutively expressed on cell surfaces whereas P-selectin is exposed on cell surface by stimuli with histamine or thrombin (Miller et al., 2014). Serum P-selectin levels were increased in patients with SAH who developed DCI, while L-selectin levels were decreased in patients with DCI (Nissen et al., 2001). Some studies showed elevation levels of E-selectin in serum and CSF after SAH (Tanriverdi et al., 2005), while others have failed to detect a higher concentration of E-selectin in the CSF of patients with SAH, even though other inflammatory molecules such as IL-6, IL-8, and monocyte chemoattractant protein-1 were elevated (Gaetani et al., 1998). Heparin and its low molecular weight derivatives are potent inhibitors of P- and L-selectins (Stevenson et al., 2005). Several clinical studies have suggested that heparin and its low molecular weight derivative enoxaparin reduce the incidence of clinical vasospasm and DCI following aneurysmal SAH (Hayman et al., 2017). Anti-E-selectin antibody also decreased vasospasm in SAH mice (Lin et al., 2005).

On the other hand, NO is released from activated glial cells during neuroinflammation (Zheng and Wong 2019). NO is synthesized enzymatically by three NO synthase (NOS) isoforms, endothelial (eNOSs), neuronal (nNOSs), and inducible NOSs (iNOSs) (Cooke and Dzau, 1997). NO provides vasodilatory and cytoprotective responses to tissues under a normal physiological state (Cooke and Dzau, 1997; van Faassen et al., 2009). However, NO is overexpressed under abnormal situations including SAH, and excess NO acts as a pro-inflammatory mediator (Miller et al., 2014). Both eNOS and iNOS were overexpressed after SAH in mice (Miller et al., 2014). The expression of iNOS is controlled by some inflammatory signaling pathways including NF-ϰB, Janus tyrosine kinase/STAT, and MAPKs signaling pathways (Pannu and Singh, 2006). Upregulation of iNOS generates excess NO and peroxynitrite, which mediate significant bystander cellular injury (Iqbal et al., 2016). Therefore, blockage of iNOS possibly presents a therapeutic option. In experimental studies, a selective iNOS inhibitor, aminoguanidine, alleviated cerebral vasospasm after SAH (Sayama et al., 1999; Zheng et al., 2010). In contrast, the function of eNOS is more complicated. In an animal model of SAH, simvastatin was shown to enhance the activity of eNOS and to improve outcomes via the attenuation of cerebral vasospasm (McGirt et al., 2002; Sugawara et al., 2008). On the other hand, knockout of eNOS in mice reduced the development of vasospasm, superoxide production, and Zn^{2+} release as well as microthrombosis formation and neuronal degeneration: eNOS knockout induced nNOS expression but had no effect on iNOS production (Sabri et al., 2013). This discrepancy of the action of eNOS may be explained by the "eNOS uncoupling". When eNOS is uncoupled, eNOS causes detrimental effects such as induction of neuronal apoptosis, microvascular dysfunction, and large artery vasospasm (Förstermann and Münzel, 2006). The eNOS uncoupling could be reversed by drugs like simvastatin, which has antioxidant and other protective effects that may preserve eNOS function (Förstermann and Münzel, 2006).

ETs are pro-inflammatory mediators produced by vascular endothelial cells and smooth muscle cells, and are thought to contribute to the development of tissue inflammation and cerebral edema (Miyauchi and Masaki, 1999). Some studies demonstrated that ET-1 levels in CSF correlated with the hemorrhage volume in the cisterns and were increased in patients with symptomatic vasospasm following SAH (Seifert et al., 1995; Mascia et al., 2001; Jung et al., 2012). However, other studies found neither significant elevations of ET-1 in the plasma and CSF nor a correlation between CSF

ET-1 levels and vasospasm after SAH (Hamann et al., 1993; Jung et al., 2012). Experimental findings were similar to clinical findings as to ET-1 (Miller et al., 2014). Overexpressed ET-1 in transgenic mice caused more pronounced cerebral vasospasm and cerebral edema, and an ET-A receptor antagonist ameliorated cerebral vasospasm and cerebral edema after SAH (Yeung et al., 2013). In addition, inhibition of both ET-1 and ET receptors exerted neuroprotective effects via attenuation of cerebral vasospasm (Siasios et al., 2013). However, other studies did not show beneficial effects of ET-1 antagonists and ET-A receptor antagonists against post-SAH neurovascular events (Miller et al., 2014).

Contribution of MCPs to neuroinflammation after SAH

MCPs are a component of the extracellular matrix and are currently considered to be an important inducer of inflammatory reactions (Liu et al., 2018; Nishikawa and Suzuki 2018). MCPs have a number of characteristics, as follows (Suzuki et al., 2020). First, MCPs are secreted and soluble proteins controlled by many stimuli, although the expression levels are low in a steady-state condition in adult tissues in general. Second, MCPs appear in almost any tissue and cell type under the specified conditions in space and time. Third, MCPs have a variety of functions through binding to receptors, other matrix proteins, growth factors, and cytokines. The functions include controlling of cellular morphology and behavior (differentiation, migration, and survival or apoptosis), modulation of the molecules' functions or cellular responses to the molecules at the plasma membrane, intracellularly, in body fluids or the extracellular matrix, and acting as reservoirs of the molecules. Fourth, knockout of MCPs in mice undergo normal development. Accumulating evidence suggests that many kinds of MCPs such as TNC, osteopontin, galectin-3, and periostin contribute to the aggravation or improvement of neuroinflammation after SAH (Murphy-Ullrich and Sage, 2014; Kanamaru et al., 2019a; Suzuki et al., 2020).

TNC typically forms a hexamer (Suzuki et al., 2020). However, alternatively spliced fibronectin type-III repeats, post-translational modifications, and proteolytic processing cause the production of many isoforms, and affect neuronal functions (Suzuki et al., 2018). TNC is upregulated at the site of tissue damage including SAH and is expressed in spastic cerebral arteries (endothelial, smooth muscle, adventitial, and periarterial inflammatory cells) and brain tissues (astrocytes, neurons, and brain capillary endothelial cells), possibly resulting in aggravation of neuroinflammation and cerebral vasospasm after SAH (Shiba et al., 2014; Shiba and Suzuki, 2019; Suzuki and Kawakita, 2016). To make matters worse, TNC may amplify the expression levels of TNC by positive feedback loops utilizing TLR4 signaling pathway in SAH, because TNC itself is one of the ligands of TLR4 (Midwood et al., 2009; Okada and Suzuki, 2017). In experimental studies, an intracisternal injection of TNC activated MAPKs and caused prolonged cerebral artery constriction via TLR4 and epidermal growth factor receptor in healthy rats (Fujimoto et al., 2013, 2015, 2016a). Knockout of TNC in SAH mice showed fewer inflammatory cell infiltrations in the subarachnoid space via suppression of TLR4/NF-κB/IL-1β, IL-6, and MMP-9 signaling pathway (Fujimoto et al., 2018; Liu et al., 2018; Shiba and Suzuki, 2019). In addition, blockage of TNC induction by imatinib mesylate attenuated neurological impairments and prevented activation of MAPKs including ERK1/2, JNK, and p38 in brain after SAH in mice (Suzuki and Kawakita, 2016). In clinical settings, a selective inhibitor of phosphodiesterase type III, cilostazol, suppressed plasma levels of TNC, and prevented DCI and chronic shunt-dependent hydrocephalus, resulting in better outcomes of patients with SAH (Nakatsuka et al., 2017; Suzuki et al., 2019). Cilostazol is an antiplatelet drug and a peripheral artery vasodilator with pleiotropic actions including the inhibition of inflammatory reactions, endothelial cell injuries, and phenotypic transformation of smooth muscle cells in cerebral arteries (Suzuki et al., 2019). Endogenous TNC levels in the CSF peaked immediately after SAH, while the plasma TNC levels peaked between 4 and 6 days in patients with SAH (Suzuki et al., 2018). Higher levels of TNC in CSF were associated with worse admission clinical grades, more massive SAH volume on computed tomographic scans at admission, higher incidences of angiographic vasospasm or DCI, and worse outcomes (Suzuki et al., 2018). The findings suggest that severe SAH or EBI may induce higher expression of TNC, and that TNC levels in CSF may be a useful biomarker to predict the development of angiographic vasospasm and DCI (Suzuki and Kawakita, 2016; Nishikawa and Suzuki, 2017).

Osteopontin is a secreted glycosylated phosphoprotein that can bind to several integrin receptors including avβ1, αvβ3, αvβ5, α4β1, α5β1, α8β1, α9β1, and CD44 (Ellison et al., 1999; Takada et al., 2007). Osteopontin is expressed in response to injury, stress, and inflammation in various cells, and is involved in homeostasis, angiogenesis, and immune responses (Rogall et al., 2018). In a rat model of SAH, osteopontin is induced in reactive astrocytes and capillary endothelial cells and peaks at 72 h post-hemorrhage (Liu and Suzuki. 2018). Osteopontin may exert neuroprotective effects against post-SAH EBI via the following multiple mechanisms: 1) suppression of microcirculatory dysfunctions via stabilizing vascular smooth muscle cell phenotypes through the activation of integrin-linked kinase/Rac-1 signaling pathways; 2) inhibition of neuronal apoptosis through integrin-mediated activation of phosphoinositide 3-kinase (PI3K)/Akt signaling pathway; 3) prevention of BBB disruption through integrin-mediated inactivation of NF-κB/MMP-9 and MAPKs/MMP-9 and/or vascular

endothelial growth factor-A signaling pathways, or via CD44 splicing-mediated glycosylated P-glycoprotein in brain capillary endothelial cells; and 4) suppression of neuroinflammation by the downregulation of iNOS/MMP-9, providing the molecular link between degradation of the extracellular matrix and tissue remodeling (Liu and Suzuki, 2018; Wu et al., 2011). In experimental models of hemorrhagic stroke, recombinant osteopontin prevented the expression of iNOS and MMP-9, and suppressed the degradation of ZO-1, reducing brain edema and improving neurobehavioral status (Wu et al., 2011). Recombinant osteopontin also suppressed the Stat1 phosphorylation and the expression of iNOS, causing the inhibition of MMP-9 induction in intracerebral hemorrhage mice (Wu et al., 2011). In addition, recombinant osteopontin increased an endogenous MAPK inhibitor, MAPK phophatase-1, in cerebral artery smooth muscle cells via binding to L-arginyl-glycyl-L-aspartate-dependent integrins in SAH mice (Wu et al., 2011; Kawakita et al., 2019). Interestingly, osteopontin seems to act as an antagonist of another matricellular protein TNC in the setting of SAH (Nishikawa and Suzuki, 2017). This may be because osteopontin binds to TNC's receptors competitively owing to sharing some receptors with each other (Suzuki and Kawakita, 2016). Clinically, plasma osteopontin levels were increased and peaked between 4 and 6 days post-SAH, and higher plasma levels of osteopontin were an independent predictor of 3-month poor outcomes in patients with aneurysmal SAH (Nakatsuka et al., 2018).

Galectin belongs to the β-galactoside-binding lectin superfamily composed of 1 or 2 carbohydrate-recognition domains (CRDs) (Elola et al., 2007; Jayakumar et al., 2017). Galectin-3 is the sole member of chimera-type galectin, and comprises one CRD and one N-terminal non-CRD for carbohydrate binding (Nishikawa and Suzuki, 2018). Galectin-3 acts as a TLR4 ligand through its CRD and activates the downstream signaling (Burguillos et al., 2015). In a mouse model of SAH, galectin-3 was upregulated in brain capillary endothelial cells, and activated MAPK ERK1/2 and STAT-3 via TLR4 (Nishikawa et al., 2018a). A galectin-3 inhibitor, citrus pectin, attenuated BBB disruption via inactivation of TLR4-ERK1/2-MMP-9 signaling pathways (Nishikawa and Suzuki, 2018; Nishikawa et al., 2018a). In a clinical setting, higher levels of plasma galectin-3 on admission were correlated with worse clinical grades on admission and poorer 6-month outcomes in patients with aneurysmal SAH, and plasma galectin-3 levels on days 1-3 post-SAH were an independent predictor of the development of DCI, regardless of the presence or absence of cerebral vasospasm (Liu et al., 2016; Nishikawa et al., 2018b).

Periostin is a N-glycoprotein with a N-terminal cysteine-rich EMI domain, fourfold repeated fasciclin I (FAS1) domain in the middle, and a hydrophilic C-terminal alternative splicing domain (Nishikawa and Suzuki, 2017; Kanamaru et al., 2019a,b). Periostin is highly secreted by stromal cells, which are stimulated by TGF-β and other local cytokines or growth factors that are produced by epithelial cells and other cells (Liu et al., 2014). An experimental study demonstrated that periostin was induced in brain capillary endothelial cells and neurons in cerebral cortex at 24 h after SAH induction (Liu et al., 2017). Periostin variants may exert different functions by directly binding to various extracellular matrix components such as fibronectin, collagens, heparin, and TNC through the C-terminal region (Norris et al., 2008; Kii et al., 2010; Shiba et al., 2014; Fujimoto et al., 2016b). Periostin also directly interacts with integrins and TNC through its FAS1 domains (Liu et al., 2014; Kudo, 2017). Periostin induces TNC expression, and vice versa (Kawakita and Suzuki, 2020). Both periostin and TNC cause BBB disruption via MAPKs signaling pathway (Kawakita and Suzuki, 2020). Neutralization of periostin prevented BBB disruption and post-SAH TNC induction, which were aggravated by administration of recombinant periostin (Liu et al., 2017). Anti-periostin antibody alleviated post-SAH BBB disruption, brain edema, and neurobehavioral impairments via downregulation of TNC, inactivation of MAPKs including p38 and ERK1/2, and downregulation of MMP-9, resulting in the retention of ZO-1 (Liu et al., 2017). On the other hand, knockout of TNC in mice inhibited post-SAH periostin induction and neurobehavioral impairments (Liu et al., 2017). The interaction between periostin and TNC would play an important role in post-SAH EBI and provide a new insight for future research (Liu et al., 2017). With regard to receptors of periostin, integrins αvβ1, αvβ3, αvβ5, and α6β4 have been reported in cardiac and cancer cells (Horiuchi et al., 1999; Bonnet et al., 2016). However, to our best knowledge, no study has examined the relationships between periostin and the specific integrin subtypes in cerebrovascular diseases. Periostin binds to integrins, leading to neuroinflammation and BBB disruption via activation of MAPKs and upregulation of MMP-9 in experimental SAH (Kawakita and Suzuki, 2020). In contrast, binding of periostin to integrins also induces neurogenesis via activation of PI3K/Akt signaling pathways and upregulation of anti-inflammatory cytokine TGF-β (Kawakita and Suzuki, 2020). In clinical settings, higher serum levels of periostin on admission were related to worse initial neurological status, larger hemorrhage volume, more frequent development of DCI and poorer outcomes in patients with aneurysmal SAH (Luo et al., 2018). In addition, plasma periostin levels increased preceding the development of DCI irrespective of the presence or absence of cerebral vasospasm (Kanamaru et al., 2019b; Kawakita and Suzuki, 2020). Therefore, peripheral blood levels of periostin may be one of biomarkers to predict the development of post-SAH DCI irrespective of the development of cerebral vasospasm.

Conclusions

Neuroinflammation is one of the most common causes of brain injury in SAH, and some studies indicate that targeting neuroinflammation would be a therapeutic option (Lucke-Wold et al., 2016). In contrast, other clinical studies have found that modulating inflammation following SAH has no beneficial effects (Lucke-Wold et al., 2016). It is likely that inflammatory signaling pathways and mediators act as protective or detrimental responses at different phases. Indeed, microglia/macrophages are also involved in clot phagocytosis in hemorrhagic stroke (Zhao et al., 2009; Aronowski and Zhao, 2011; Hammond et al., 2014; Keep et al., 2018). Interestingly, monocytes played a role in tissue repair and hematoma phagocytosis in hemorrhagic stroke, while depletion of inflammatory monocytes reduced brain damage in hemorrhagic stroke (Zhao et al., 2009; Aronowski and Zhao, 2011, Hammond et al., 2014; Keep et al., 2018). Monocytes are comprised of two populations: CCR2+Ly6Chi and CX3CR1+Ly6C−. The former exerts inflammatory effects at perihematomal brain tissue, while the latter patrols the endothelium of blood vessels and is considered to have a healing role (Hammond et al., 2014). Thus, it is important to suppress neuroinflammation without preventing neuroprotective immunoreaction. Tailoring therapy to match the timing and intensity of an individual patient's inflammatory response would need to be developed in the future.

On the other hand, at clinical practice, it is much more difficult to assess neuroinflammation compared to large-vessel vasospasm. To predict or diagnose early a risk of EBI and DCI after SAH, reliable biomarkers should be explored (Geraghty et al., 2019). Peripheral blood levels of MCPs may be good candidates for guiding us to diagnose neuroinflammation earlier (Suzuki et al., 2018; Tanioka et al., 2019). To elucidate the appropriate inflammatory biomarkers and the mechanisms of neuroinflammation after SAH, further in vivo and in vitro investigations should be implemented with meticulous study designs (Suzuki and Nakano, 2018).

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